REMARKS

Claims 1-14 and 21-40 were pending in this application. No claim has been allowed. Claims 1-14 and 21-40 are currently pending.

Invention

The invention relates to the use of prostate antigens or their representatives in vaccines to produce an immune response to prevent or treat cancer. While the prior art suggests the use of antigens uniquely associated with tumor tissue as components of antitumor vaccines, there is no suggestion to use antigens which are uniquely represented on host tissue for the tumor. Since the prostate is not an essential organ, elimination of the prostate gland, which may be a concomitant effect of the vaccines of the invention, does not adversely impact the general health of the subject. Thus, prostate cancer offers a unique opportunity for treatment with vaccines using antigens that characterize the host organ itself, rather than the malignant or metastatic nature of the cells *per se*.

Further, although it is recognized that prostate specific antigen (PSA) can be used in healthy experimental animals to generate antibodies for use in diagnosis, there is no suggestion that PSA or any other prostate antigen be used to elicit a protective or therapeutic immune response against prostate cancer.

Rejection Under 35 U.S.C. § 112, first paragraph - Written Description

Claims 1-14 and 21-40 are rejected under 35 U.S.C. 112, first paragraph as allegedly failing to sufficiently describe the claimed subject matter so as to reasonably convey to the skilled artisan that the inventors had possession of the subject matter at the time the application was filed. The Action asserts that "overrepresented antigens or immunologically effective portions thereof", "nucleic acid that generate said antigen or antigens in situ" as well as a "protein" or "peptide" is

insufficiently described for reasons of record. Applicants traverse this rejection for reasons of record and those discussed *infra*.

1. The specification sufficiently describes a number of representative species, satisfying the written description requirement for the claimed genus.

Applicants respectfully submit that the species described in the specification reasonably convey to the skilled artisan the possession of the claimed genus of overrepresented antigens and immunologically effective portions thereof at the time of filing. A description of every species within a claimed genus is not required. *See* MPEP § 2163 (II)(A)(3)(ii) ("Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species the genus embraces."). The representative species, PSA, PMSA, and PAP, are fully described at page 7, line 11 to page 10, line 2. These disclosed species are illustrative of the claimed genus of overrepresented antigens in their identifying relevant properties - they are uniquely and highly expressed on prostate tissue. *See* the specification, at page 9, line 30 to page 10, line 2 and page 5, lines 15-27. Such a pattern of expression is a physical characteristic of the antigen easily determined using well known and routine methods in the art, *e.g.*, immunohistochemical staining or flow cytometric analysis. Moreover, it is the pertinent characteristic that defines the antigens useful in the claimed methods. Applicants emphasize that the patentability of the claimed methods lies not in the novelty of PAP, PSMA, PSA, or other antigens that are uniquely expressed on prostate tissue, but rather in knowing what to do with the antigens. In other words, the patentability lies in the novelty of the method disclosed and not the antigens themselves. Therefore, the description of the relevant, identifying characteristic, *i.e.*, unique expression in prostate tissue and the disclosure of three representative species in the claimed genus reasonably conveys that Applicants had possession of the claimed methods at the time of filing, thus fulfilling the written description requirement.

2. The description of the nucleic acid sequences meets the written description requirement.

Applicants respectfully submit that the nucleic acid sequences are sufficiently described in the instant specification to reasonably convey possession of the genus of nucleic acid sequences to the skilled artisan. As noted above, an adequate description of a representative number of species is sufficient. In addition, Applicants note that the legal standard for the written description requirement for genetic material does not require a greater amount of description than other inventions. In other words, an explicit disclosure of a DNA sequence is not necessarily required. The amount and type of required description is determined by the understanding of one of ordinary skill in the art. *Amgen Inc. v. Hoechst Marion Roussel, Inc.* 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003)(noting that "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure").

First, the representative antigens and their corresponding nucleotide sequences are well known. The specification discloses PSA, its expression profile, functional identity (*i.e.*, protease in the glandular kallikrein family), its chemical structure, and cites publications containing the amino acid and nucleotide sequences at page 8, lines 1 to page 9, line 2. PAP is disclosed in the specification as a "widely studied antigen" at page 7, lines 21-23. The specification also discloses that the nucleotide sequence of PAP is known and cites two publications that disclose the sequence of this antigen. *See* specification, at page 8, lines 1-5. Similarly, PSMA is disclosed as a known and well-characterized antigen at page 9, lines 9-27 of the instant specification. Appellants also disclose that the nucleotide sequence of PSMA is known and cite a publication that discloses this sequence. *See* specification, at page 9, lines 9-11. Therefore, the disclosure in the specification reasonably conveys possession of the representative species of the claimed genus to one of ordinary skill in the art.

Second, the patentability of the instant methods lies not in the invention of the antigens uniquely expressed on prostate tissue or their encoding DNA sequences, but rather in knowing what to do with the antigens. Again, the patentability lies in the novelty of the method disclosed and not the antigens themselves. Appellants respectfully submit that the Office is improperly applying the written description requirement as if the claimed invention were a novel DNA sequence. While the demonstration of the conception and reduction to practice of a novel DNA sequence does require the identification of the actual DNA being claimed, it does not follow that the requirement for the recitation of a DNA sequence is applicable to claims involving a method using known proteins and DNA sequences where the patentability lies in the method itself and the sequences are available in the art. As stated above, the Federal Circuit has recently affirmed that all functional descriptions of genetic material do not necessarily fail as a matter of law. *Amgen*, at 1398. Rather the knowledge in the art and the disclosure must be such that one of ordinary skill in the art would comprehend that the applicants had possession of the invention at the time of filing. Appellants submit that the knowledge in the art regarding these proteins and their encoding sequences and the disclosure of this information in the specification is sufficient to convey to the skilled artisan that the Appellants had possession of the genus of uniquely expressed prostate antigens at the time of filing. Therefore, the specification fulfills the written description requirement of 35 U.S.C. § 112.

4. The specification adequately describes "protein" and "peptide."

Applicants submit that the adequate description of three representative antigens, each of which is a protein, is sufficient to reasonably convey to one of skill in the art the possession of protein antigens with the identifying characteristics of the claimed genus. A description of each and every protein antigen useful in the claimed methods is not required, and therefore the description of the three representative antigens, each of which are proteins and the relevant, identifying characteristics is sufficient. Moreover, the specification discloses the production of peptides using well known methodology at, *e.g.*, page 11, lines 30 - page 12, line 19. Again, the patentability of the

claimed methods is knowing what to do with the antigens, not the novelty of any one protein or peptide.

In light of the above, the basis of the rejection may be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 1-14 and 21-40 are rejected under 35 U.S.C. 112, first paragraph as allegedly lacking enablement in the specification as filed for reasons of record. Specifically, the Action asserts that the specification does not provide reasonable enablement for any "overrepresented prostate specific antigen", "immunologically effective portion thereof", "protein", or "peptide." Applicants traverse this rejection for reasons of record and those discussed *infra*.

1. The submitted evidence definitively supports the claimed methods.

Applicants respectfully submit that sufficient objective evidence submitted adequately predicts the efficacy of the claimed methods using overrepresented prostate antigens and immunologically effective portions thereof. First, the specification discloses the identifying, relevant characteristics genus of antigens useful in the claimed methods. The identifying, relevant characteristics are that these antigens are uniquely and highly expressed by prostate tissue. *See* the specification, at page 9, line 30 to page 10, line 2 and page 5, lines 15-27. Applicants notes that identifying biochemical information is not a requirement for identifying the genus of antigen. The requirement can be biochemical or physical. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 U.S.P.Q.2d 1609, 1613 (2002). As discussed above, the relevant physical characteristic is identified in the specification. Second, the specification discloses representative species in the genus, namely PSA, PAP, and PSMA. Third, Applicants have provided objective evidence that the claimed methods perform as described, *i.e.*, elicit an effective antitumor response. As stated in the MPEP § 2164.03:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would

expect the claimed genus could be used in that manner without undue experimentation.

Applicants submit that the requirement under 35 U.S.C. § 112, first paragraph because the genus is adequately identified, representative species named, and overwhelming evidence of record in this application demonstrates that the claimed methods performs as described.

2. Applicants respectfully submit that the reasons advanced by the examiner supporting the non-enablement rejection are not adequate.

Applicants respectfully submit that "proof of enablement [is] required for other members of the claimed genus only when adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation (emphasis added)." MPEP § 2164.03. The Examiner asserts that a disclosure of "how to use" the claimed methods is absent, and that the art suggests that *in vivo* applications are unpredictable. Applicants submit that these reasons are not supported by the arguments set forth in the Action and therefore these reasons do not support a requirement for additional proof of enablement.

First, the specification fully discloses how to use the claimed invention. Moreover, the evidence submitting demonstrating the efficacy of the claimed methods uses the guidance provided in the specification. The disclosure of how to use is discussed in detail in Paper No. 32, pages 13-14. As Applicants are not required to enumerate every member of a claimed genus if representative species are identified, the disclosure in the instant application fully enables the claimed methods.

Second, as previously stated, any experimentation required to practice the claimed methods is routine. The specification teaches all of the steps required for practicing the proven claimed invention, and all that remains is repetition of these teachings to practice the scope of the claims. The claimed methods have been carried-out according to the teachings of the specification using a representative species, PSA, as an antigen and result in an effective antitumor immune response. Repeating vaccine studies for different antigens, including full-length polypeptides, portions of those polypeptides, and nucleic acids that express the foregoing polypeptides *in situ*, is routine. The

routine nature of identifying and using immunogenic peptide is confirmed by each of the experts in the declarations of record. To date, the Examiner has not indicated why these declarations are deficient or provided evidence that outweighs the sworn statements of skilled artisans in the art. As the claimed methods can be easily practiced by a person of ordinary skill in the art with only routine experimentation, any experimentation required for practicing the claimed methods would not be undue.

Third, the determination of whether a disclosure is fully enabling is governed by the view of one of skill in the art, not the Examiner. *See* MPEP § 2164.03. The Examiner has yet to address why the declarations of Drs. Mastrangelo, Bystryn, Livingston, and Oldham are deficient as representative views of one of skill in the art. As discussed in Paper No. 32, these skilled artisans opine that other antigens with similar characteristics, *i.e.*, being expressed on prostate tissue, should behave in the same way. Applicants again request a detailed explanation of why this evidence is deficient.

Fourth, sound scientific reasoning does not support the reasons set forth by the Examiner to maintain a requirement of additional proof of enablement. The statements used from Hodges by the Examiner describe a completely distinct system. The Examiner cites language concerning tumor vaccines employing whole tumor cells as the source of the eliciting antigen. The skilled artisan readily distinguishes vaccines using whole cells and purified antigens as completely different on the basis of fundamental and well known immunology principles. First, the whole cell antigen can act as its own antigen presenting cell. As the Office undoubtedly recognizes, the elicitation of immune response using antigen presenting cells that are MHC-mismatched at one or more loci results in a fundamentally different response that can be less antigen specific, of shorter duration, and thus ultimately less effective. The antigen of the claimed methods, on the other hand, employs self antigen presenting cells, permitting the maximal elicitation of an antigen-specific response. A skilled artisan does not equate cell-based vaccines with purified antigen-based vaccines. Applicants

request sound scientific reasoning demonstrating that such vaccines would be equated by a skilled artisan.

Finally, the objective evidence of record demonstrates that the use of prostate-specific antigens is effective and is not limited by cross-reactivity or autoimmunity. On page 8 of Paper No. 33, the Examiner asserts that "the use of prostate-specific antigens in vaccines are likely to be limited by either neutralization by secreted prostate antigen or by inducing autoimmunity." The Examiner goes on to specifically look to PSA responses in Hodge. First, Applicants submit that the objective evidence submitted demonstrates the effective use of PSA as a tumor vaccine. In five separate clinical trials, no evidence of neutralization by secreted prostate antigen or autoimmunity was found. This data is sufficient to convey to one of skill in the art that the claimed methods work. Applicants request that the Examiner state why this evidence is not considered in the cited analysis.

In light of the above, the basis for this rejection may be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for reasons of record. In particular, the Action alleges that the term "overrepresented" is indefinite. Applicants traverse this rejection for reasons of record and those discussed *infra*.

Applicants submit that the term "overrepresented" is sufficiently definite in light of the disclosure in the specification because one of skill in the art would understand the term. MPEP § 2173.05(b) ("Acceptability of the claim language depends on whether one of skill in the art would understand what is claimed in light of the specification."). First, the specification provides a standard for measuring the expression of antigen in prostate tissue relative to other tissues at page 5, lines 15-27 in terms of overall clinical toxicity. The specification further states that the expression of these antigens must be such that the prostate tissue can be distinguished from other tissue by

virtue of the presence of the antigen. *See* page 9, line 30 to page 10, line 2. From this disclosure, the skilled artisan recognizes the "overrepresented antigens" as those expressed uniquely on prostate tissue and not in other organ systems. If the Examiner's rejection is based on facts within his personal knowledge regarding the inability to determine which antigens are uniquely expressed on one tissue and not on another, the Examiner is requested to provide a specific and factual basis to support this assertion.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-14 and 21-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spitler in view of Israeli *et al*, Horoszewicz, Andriole *et al.* and in view of art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley *et al.* Applicants traverse this rejection for reasons of record and those discussed *infra.*

1. Spitler teaches the use of a pan-antigen in active immunotherapy of tumors.

Spitler specifically provides for a vaccine composition useful in treating "all forms" or "a variety" of cancers and enables this teaching using antigens that are expressed on a number of different and unrelated malignancies, and therefore teaches the use of a pan-antigen. At column 1, lines 45-51 states:

> Almost all forms of cancer continue to be refractory to treatment despite many years of therapeutic experience. Vaccine development has been slow and no vaccine currently exists for any form of cancer. There is, therefore, a continuing need for the development of new and therapeutic and prophylactic compounds efficacious in the prevention and treatment of all forms of cancer" (emphasis added).

This passage does not state that a vaccine directed to a single form of cancer is available or even desirable. Rather, the disclosure teaches that there is a need for a vaccine that can treat all cancers. Spitler again restates this objective in the "Summary of the Invention" that "[t]he compositions are

useful as vaccine-like compounds for the prevention and treatment of a variety of cancers" (emphasis added). See Spitler, Column 2, lines 19-21. The emphasis of using a pan-antigen as a vaccine composition is further observed in Spitler's selection of antigens useful. For example, at column 2, lines 21-26, Spitler states:

> Of particular interest are liposome compositions encapsulating the TAAs, CA-029, associated with tumors of the gastrointestinal tract, colorectum, and pancreas and GA733-2, associated with tumors of the gastrointestinal tract, prostate, cervix, ovary, bladder, lung, breast, colorectum, and pancreas.

Notably, each of the two representative antigens is expressed on multiple different and unrelated tumors. Moreover, the antigens cites as exemplifications of useful antigens in Spitler are largely those antigens widely expressed in a variety of different and unrelated tumors. *See* Column 4, lines 7-21. For example, one of the the antigens cited by Spitler, CEA (carcinoembryonic antigen), is recognized as being widely expressed on a variety of malignant cells. Moreover, the antigen bound by CO 17-1A and KS 1/4 is EpCam, the same antigen bound by GA733-2. Therefore, Spitler plainly teaches the use of an antigen that is expressed by a variety of malignant cells. There is no teaching of using prostate-specific antigens or antigen expressed by normal prostate tissue. In view of the absence of such disclosure regarding organ-specific antigens and the clear teaching away from the claimed methods, Spitler does not render the claimed method obvious in combination with any of the cited references.

2. Publications teaching passive immunotherapy do not convey any knowledge regarding active immunotherapy and useful antigens therein.

Applicants again respectfully submit that the usefulness of prostate antigens in generating antibodies capable of binding sufficiently to be useful in diagnostic and toxin delivery methods does not convey any information regarding the usefulness of these antigens in eliciting an active and effective immune response against prostate cancer. As discussed *supra*, Spitler does not teach the use of organ-specific antigens to elicit responses. Therefore, the motivation to combine Spitler with

any of the cited references requires that teachings regarding passive immunotherapy reasonably convey to the skilled artisan that these organ specific antigens would be useful in an active immunotherapy/vaccine strategy. Such motivation must be found in the references themselves or in the art. MPEP § 2143. The Examiner has pointed to teachings regarding the isolation and expression of PSMA DNA (Israeli), the need for specific antibodies (Horoszewicz and McCarley), and the use of surgery in cancer therapy (Andriole). None of these references suggest or teach that a substitution of an organ-specific antigen is useful or desirable in an active immunotherapy/vaccine protocol because none of the references even contemplates active immunotherapy. In the absence of a reference showing that one of skill in the art equates the teachings regarding passive and active immunotherapy, the combination set forth by the Office is unsupported. If the Examiner's rejection is based on facts within his personal knowledge regarding the motivation to take teachings limited to passive immunotherapy and apply them to active immunotherapy protocols, the Examine will support this rejection with an affidavit by the Examiner according to MPEP § 2144.03. According to MPEP § 2144.03,

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner.

3. The Action mischaracterizes Applicants' arguments regarding passive and active immunotherapy.

Applicants do not rely on the statement that "any one tumor antigen that can elicit an immune response of any kind" in the arguments regarding the enablement of the claimed methods. This is completely incorrect and reflects the continued, substantive misunderstanding of the distinction between passive and active immunotherapy. First, contrary to the Examiner's assertions, the specification provides for a genus of antigens with a defined, relevant characteristic for use in an active immunotherapy protocol. Neither Applicants nor the specification assert that the class of antigens useful in the claimed methods are any antigens. Rather the antigens useful in the claimed

method are a discrete class of antigens fully disclosed in the specification, illustrated by three representative species, and recognized as a genus by one of skill in the art. *See* Declarations of Mastrangelo, Bystryn, Livingston, and Oldham submitted May 7, 1998. The statements made by Applicants asserting that "all tumor antigens are not alike" address the irrelevancy of the immunogenicity, and subsequently its usefulness in a vaccine, of antigens expressed on a variety of tumors to the immunogenicity, and subsequently the usefulness in a vaccine, of organ-specific antigens. Applicants note that the immunogenicity of organ-specific antigens, particularly those expressed in normal tissue, is believed to be very low as a result of self-tolerance. Hence, it is unexpected that such antigens would be useful or effective in a vaccine strategy. Therefore, on its face, the disclosure in Spitler conveys no relevant information regarding the use of organ specific antigens. Again, it is the identification of this class of antigens (*i.e.*, overrepresented prostate antigens) for use in these methods that constitutes the patentability of the claimed methods.

In light of the above, the basis for this rejection may be withdrawn.

Obviousness-Type Double Patenting Rejections

Claims 1-14 and 21-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent 5,925,362. Claims 1-14 and 21-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 15, 16, and 18-24 of copending application Serial No. 09/300,978.

Applicants respectfully request that these rejections be held in abeyance until allowable subject matter is indicated in the instant application.

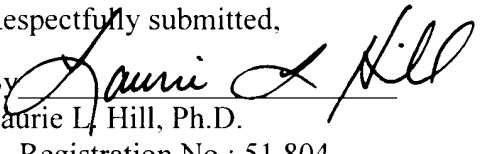
CONCLUSION

Applicants submit that the rejections under 35 U.S.C. §§ 112 and 103 have been overcome by the above remarks. Early allowance of pending claims 1-14 and 21-40 is respectfully requested. If the Examiner thinks an telephonic conference would be helpful, please call the undersigned at (858) 720-7955 at your convenience.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or fees due in connection with this document to **Deposit Account No. 03-1952** referencing docket no. 204372000300.

Dated: August 11, 2003

Respectfully submitted,

By 

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